Hepatic Encephalopathy Update:
Reports From the American Association for the Study of Liver Diseases Annual Meeting, 2011

HEPATOLOGY Centers of Educational Expertise

Project ID: 11-0014-NL-4

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Objectives:

- Identify predictors of hepatic encephalopathy (HE) in patients with cirrhosis and determine appropriate prophylactic regimens for such patients
- Evaluate the use of breath sample analysis to diagnose HE
- Describe specific bacteria that are related to cognition and inflammation in HE
- Determine additional problems that may be associated with neuropsychiatric impairment in HE and assess appropriate screening tools to diagnose these conditions
- Analyze the development of and treatment with portosystemic shunts in HE

Hepatic encephalopathy (HE) is a largely studied complication of cirrhosis because it continues to be a major cause of morbidity in cirrhotic patients. Oral presentations and poster sessions from the American Association for the Study of Liver Diseases (AASLD) 2011 meeting focused on prevention measures for HE, such as identifying predictors and determining appropriate prophylactic regimens. In addition, new diagnostic techniques were evaluated, symptoms related to HE were analyzed, and the development of and treatment with portosystemic shunts were discussed. This newsletter will summarize selected presentations that cover these topics.

Predicting HE in Cirrhotic Patients

HE is a major complication of cirrhosis, but it can be pharmacologically prevented. Therefore, identifying predictors of HE in cirrhotic patients is useful in determining candidates for prophylactic therapy. Nardelli and colleagues analyzed a large cohort (N=177) of cirrhotic patients over 2 years, with a mean follow-up of approximately 11 months, to identify predictors of overt (O) HE.[1] Patients were included in the evaluation if they had no evidence of dementia, as indicated by a mini mental state examination score higher than 26, or overt encephalopathy, determined by West Haven Criteria and CHESS scores. Minimal (M) HE was detected using a simplified psychometric hepatic encephalopathy score (SPHES), consisting of 3 psychometric tests (digit symbol, serial dotting, and line tracing) and was found to be present in approximately half of the patients (N=87; 50.8%). Previous bouts of OHE occurred in 24% of patients (N=40).

During follow-up, one third of patients (N=57) experienced at least 1 bout of overt HE (Figure 1), which occurred in 47% of patients with minimal HE and 60% of patients with a history of OHE. Both MHE and a history of OHE were found to increase the risk of OHE (3.88 times and 4.98 times, respectively). Since 73% of patients with MHE also had a history of OHE, a Cox multiple regression analysis was performed to take into account this parameter along with age, Child Pugh score, and SPHES. This analysis determined that the only parameters that were independently related to the development of OHE were the presence of MHE and the severity of liver failure. The results of this analysis led the authors to conclude that patients with MHE should be considered for treatment to prevent OHE.

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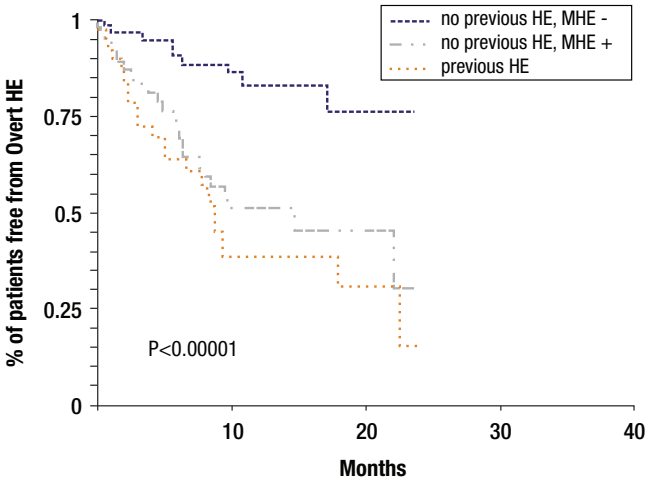

Figure 1: Proportion of patients free from overt HE simulation and cognitive testing in cirrhotic patients.

Another predictor of HE may be the presence sarcopenia. In cirrhosis, hepatic ureagenesis for ammonia disposal is reduced, increasing the demand on the skeletal muscle for disposal of ammonia and aggravating hyperammonemia. Since hyperammonemia is the principal mediator of HE and is also an element of sarcopenia, Periyalwar and colleagues hypothesized that sarcopenia aggravates the frequency and severity of HE cirrhosis.[2]

This hypothesis was investigated by prospectively evaluating 101 patients with cirrhosis, 46 patients with non-cirrhotic liver disease (NCLD), and 32 healthy controls. Patients in this study underwent body composition evaluations, using anthropometric measures, grip strength, subjective global assessment (which included self-reported muscle loss), and tetrapolar bioelectrical impedance analysis. Sarcopenia was defined as skeletal muscle mass <20th percentile of that in controls. In addition, the number of episodes, severity, and frequency of HE were documented in the year prior to and year after assessment of body composition. Furthermore, clinical and psychometric tests were used to determine the severity of HE.

Among cirrhotic patients, 55 had no HE, 30 had MHE, and 16 had OHE. Midarm muscle area, skinfold thickness, and grip strength were significantly lower in cirrhotic patients (P<.01) compared to the other 2 groups, who were similar. Self reported moderate/severe muscle loss was more frequent (P<.0001) in cirrhotic patients with HE (73.3%) compared to those without HE (I8.8%). Cirrhotic patients with sarcopenia experienced more frequent hospitalizations per year, a greater number of HE episodes per year, and more severe HE compared to patients with cirrhosis without sarcopenia (Table 1). The results of this study indicate that sarcopenia is common in cirrhosis and the presence of sarcopenia in these patients predicts more frequent and severe HE.

	Cirrhotics With Sarcopenia	Cirrhotics Without Sarcopenia	*P* value
Frequency of hospitalizations per year for HE	2.4	0.8	<.001
Number of episodes of HE per year	1.9	0.3	<.001
HE grade	2.8	1.1	<.01

Table 1. Comparison of Cirrhotic Patients With Sarcopenia vs. Those Without Sarcopenia

The Use of Prophylactic Therapy to Prevent HE and Associated Complications

Once predictors of HE are identified, choosing the appropriate prophylactic regimen to prevent HE and associated complications is an important next step. Two studies presented at the AASLD meeting examined this concept. One study by Agrawal and colleagues assessed the effect of probiotics and lactulose on the development of recurrent HE.[3] Consecutive patients with cirrhosis who recovered from HE (N=235) were randomized to receive lactulose (n=80), probiotics (n=77), and no therapy (n=78). At inclusion and monthly, all patients were assessed by psychometry [number connection test (NCT-A, B), figure connection test if illiterate (FCT-A, B), digit symbol test (DST), and block design test (BDT)], critical flicker frequency test (CFF), and arterial ammonia. The primary endpoint was the development of OHE, according to West-Haven criteria, during the study or at 12-month follow-up. Overall, 197 patients completed the study (38 patients lost to follow-up) and 77 of these patients (39%) developed HE (Figure 2). Significantly more patients receiving no therapy developed HE compared to those receiving lactulose or probiotics (P=.001, .002, respectively). No significant differences were seen in the development of HE between the lactulose and probiotics groups (P=.349). Lactulose and probiotics are therefore considered effective for secondary prophylaxis of HE in patients with cirrhosis.

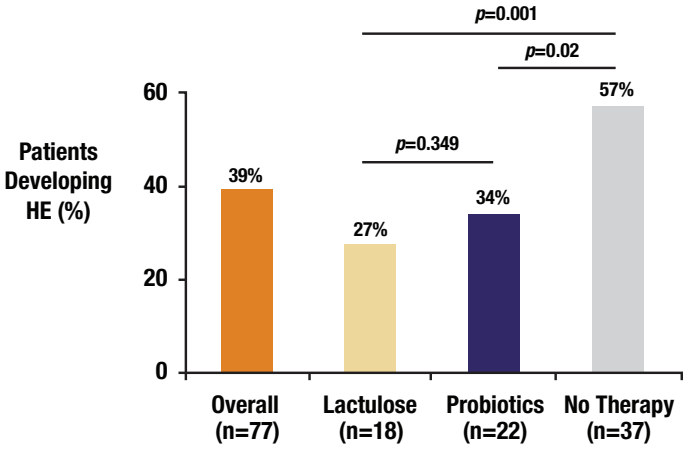

Figure 2: Secondary prophylaxis of HE with lactulose or probiotics: Patients developing HE.

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Another study by Hassett and coworkers examined the utility of rifaximin, a non-absorbable antibiotic traditionally used for the prevention of hospitalizations from HE.[4] A total of 254 patients receiving a combination of rifaximin and lactulose for > 3 months were divided into 2 groups according to model end-stage liver diseae (MELD) scores (≥20 and <20). These 2 groups were similar in terms of demographics and disease etiology (chronic hepatitis C, Laennec's cirrhosis, primary liver cancer, and nonalcoholic steatohepatitis accounted for a majority of the cohort).

Of the 220 patients with complete data, 683 hospitalizations occurred with 29% (195) due to HE. Patients with a MELD score of <20 experienced more HE-related hospitalizations per patient compared to the MELD score >20 population (2.5 vs. 1.6 respectively, Figure 3). However, patients with a MELD score >20 had greater incidence of hospitalizations per patient from non–HE-related causes (3.73 vs. 3.29 in the MELD score <20 population, Figure 3), which may be attributed to increasing severity of their liver disease. The investigators therefore concluded that the preventive effect of rifaximin and lactulose combination therapy was more pronounced in patients whose MELD scores were ≥20. They recognize that further data are needed to determine if this observation continues to hold among other patients with very advanced liver disease.

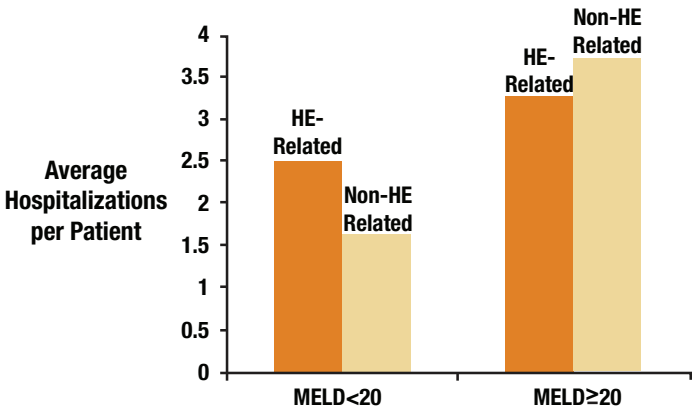

Figure 3: Average HE and non–HE-related hospitalizations per patient according to MELD score.

An Advancement in the Diagnosis of HE

The use of breath sample analysis for volatile organic compounds to diagnose HE in cirrhotic patients was recently evaluated by Halliday and colleagues.[5] This study classified patients with biopsy-proven cirrhosis as neuropsychiatrically impaired (n=10), MHE (n=6), or OHE (n=10). Breath samples were analyzed, volatile organic compounds were collected, and a chromatograph mass spectrometer identified 280 peaks to be investigated as potential markers of HE.

A number of peaks were identified in patients with cirrhosis that were absent or present in significantly different quantities in the healthy controls. Discriminant analysis was used to generate 2 classification equations using data from 12 peaks to build a predictive model for HE. This model correctly classified all patients from the original population, indicating that analysis of volatile organic compounds identifies patients with HE with a high degree of accuracy. The development of these classification equations is an exciting step in the field of HE as further evaluation of these equations in different patients may provide additional insights into the pathogenesis of HE and potential new therapeutic targets.

Microbial Causes of HE Symptomatology

It is known that HE is related to gut bacteria and inflammation with intestinal barrier dysfunction, but the specific bacteria that are behind this pathophysiology are questionable. Using a systems biology approach, Bajaj et al sought to determine which gut microbiomes are related to cognition and inflammation in cirrhotics with and without HE.[6] This patient population underwent cognitive testing; specifically, number connection (NCT A/B), DST, line drawing (LDT), serial dotting (SDT), and inhibitory control (ICT) lures/targets. Inflammatory cytokines were assessed along with endotoxin and stool multi-tag pyrosequencing. Patients on lactulose alone were compared to those on rifaximin; patients with HE were compared to those without HE.

Of the 25 patients included in the study, 17 had controlled HE (17 on lactulose, 6 of whom were on both rifaximin and lactulose) and 8 had no HE. There was evidence of altered gut microbiome (significantly higher *Veillonellaceae*, *P*=.04), significantly poorer cognition (NCT A/B and ICT lures, *P*<.01) and more endotoxemia (P=.0002) and inflammation (IL-6, TNF-alfa, IL-2, IL-13, all *P*<.01) in HE patients compared to non-HE patients. In the HE group, there was no significant difference in cognition, microbes, or inflammation in patients with or without rifaximin. In the entire group, *Alcaligeneceae* correlated with significantly worse ICT and *Porphyromonadaceae* correlated with poor ICT targets. Furthermore, *Fusobacteriaceae, Veillonellaceae* and *Enterobacteriaceae* were positively related to endotoxemia and inflammation. According to a network analysis comparison, robust correlations only existed between microbiome, cognition, IL-23, IL-2, and IL-13 (Figure 4). Therefore, in HE, a correlation exists between specific bacterial taxa, eg, *Alcaligeneceae, Porphyromonadaceae* and *Enterobacteriaceae*, and cognition and inflammation.

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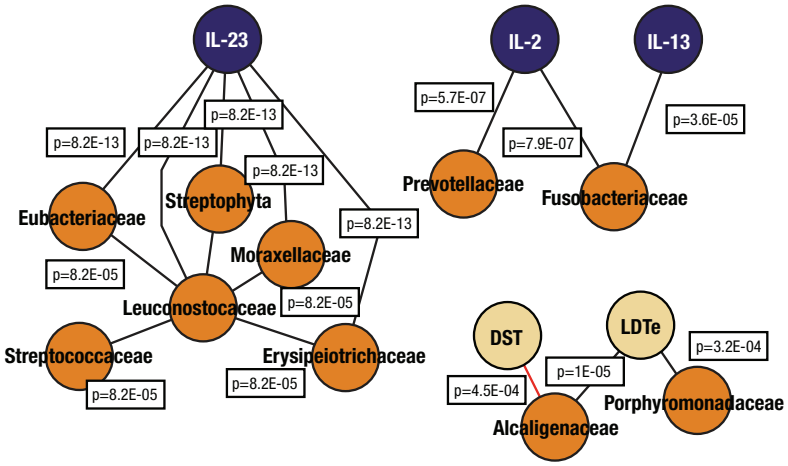

Figure 4: Correlation network analysis in HE.

Effects of HE-Related Neuropsychiatric Impairment

Neuropsychiatric impairment associated with HE may be an indicator of additional problems. For example, recent data have suggested that cirrhotic neuropsychiatric impairment might be correlated to excessive daytime sleepiness. One study by De Rui et al investigated the relationship between sleep-wake complaints and neuropsychiatric status by evaluating a group of cirrhotic patients (N=106), via yes/no questions, for the presence of excessive daytime sleepiness, difficulty falling asleep, and frequent night awakenings in their everyday lives.[7] Neuropsychiatric assessments, EEG recordings, and paper pencil psychometry (PHES) tests were also performed. Patients were evaluated at baseline and during follow-up.

Upon study entry, 37 patients (35%) had mild OHE, 33 (31%) MHE (normal clinically, abnormal PHES and/or EEG), while the remaining 36 (34%) were unimpaired. While 38 patients (36%) reported having difficulty falling asleep and 53 patients (50%) awakened frequently during the night, no association was observed between these complaints and indices of neuropsychiatric dysfunction. In contrast, the 75 patients (72%) that reported excessive daytime sleepiness demonstrated significantly slower EEGs than their counterparts without this complaint (EEG dominant frequency 9.3±2.4 vs. 10.1±2.2 Hz, *P*=.05). Furthermore, excessive daytime sleepiness was associated with the presence of portal-systemic shunt (Pearson X2=3.5, *P*<.05) and the subsequent occurrence of HE-related hospitalizations (*P*<.05). This study further validates that daytime sleepiness is in fact associated with HE and its neuropsychiatric development over time.

HE in cirrhotic patients may also affect driving performance. To validate this theory, in a study by Maheshwari et al, results of driving simulator tests from cirrhotic patients with a history of HE were compared to results in cirrhotic patients without HE and healthy controls.[8] All patients included in the study (46 cirrhotics, 17 healthy controls) also underwent psychometric testing (number connection tests; NCT and digit symbol test; DST) and CFF testing.

Although psychometric test results were significantly worse in cirrhotic patients than controls [higher NCT A (39.3 sec vs. 31.2 sec, *P*=.006) and DST scores (317 sec vs. 245 sec, *P*=.012)], these results were similar among patients with or without prior HE. CFF scores were also significantly worse in cirrhotic patients than controls (fusion: 36 vs. 42 Hz, *P*=.001 and flicker: 34 vs. 36 Hz, *P*=.04). Driving performance was not affected by HE history or CFF scores, but was affected by abnormal NCT A test results. In fact, all patients who had abnormal NCT A scores failed the pedestrian portion of the driving test vs. 64% of patients with normal NCT A scores (*P*=0.025). Therefore, abnormal NCT A scores could be a screening tool to evaluate cirrhotic patients at risk for driving errors.

New Data on Spontaneous Portosystemic Shunts

Spontaneous portosystemic shunts are a frequent phenomenon in patients with HE. Data from AASLD examine the cause-and-effect relationship between shunts and new-onset HE and whether embolizing the shunts demonstrates benefits or poses harm to patients.

Although cirrhotic patients with portal vein thrombosis (PVT) often have spontaneous spleno-renal shunts (SRS), it is unknown whether SRS is the cause or effect of PVT. Therefore, John and colleagues evaluated 243 cirrhotic patients to assess if the existence of SRS predisposes patients for the development of new PVT.[9] In addition, the role of SRS in the onset of ascites, HE, and death was assessed.

Patients were divided into 2 groups according to baseline presence (group 1, N=49) or absence (group 2, N=194) of SRS and followed for a mean of approximately 24 months. More patients with SRS at baseline developed PVT compared to patients without SRS (14% vs.8%, respectively). As determined by multi-variate analysis after adjusting for presence of ascites and creatinine, patients with SRS are not at an increased risk of developing PVT, (relative risk 1.5, 95% CI 0.61-3.7, *P*=.37). There was no difference in the development of new-onset ascites, encephalopathy, or pre- and post-transplant mortality between the 2 groups, indicating that SRS is not associated with worsening liver disease or mortality. However, patients with SRS and PVT were significantly more likely to develop HE compared to patients with SRS and PVT (50% vs. 7%; *P*=.022). Based on these results, the authors have hypothesized that the development of PVT causes blood to bypass from the portal vein to the spleno-renal shunt, resulting in HE.

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Since the development of large, spontaneous portosystemic shunts (SPSSs) is common in HE, interventions to control SPSSs may heighten quality of life in HE patients and improve the associated health-economic burden. In a study by Laleman et al, compensated cirrhotic patients with refractory HE (Table 2) and confirmed SPSSs underwent SPSS embolization.[10] Both efficacy (assessed by grade of HE and number and duration of hospitalizations within 100 days pre- and post-treatment) and short- and long-term complications (procedural and portal hypertensive-related) of this procedure were analyzed.

Recurrent episodes of HE (> grade 2 according to New Haven classification)
AND
At least 2 hospitalizations after start of standard therapy AND
Daily lactulose ± selective intestinal decontamination
OR
Persisting HE 30 days after start of standard therapy at first hospital admission (maximal grade HE > III in 90%)

Table 2. Study Definitions of Refractory HE

Ten patients were embolized for SPSS, which included recanalized paraumbilical veins (n=6), splenorenal shunts (n=3), and a shunt between the superior mesenteric and right ovarian vein (n=1). No episodes of variceal hemorrhage or renal function deterioration, procedure-related complications, transplantations, or deaths occurred post-procedure. Since embolization, there were significantly less hospitalizations (2 episodes per 100 days pre-embolization vs. 15 episodes per 100 days post-embolization, *P*=.01) and days spent in the hospital due to HE (47 days pre vs. 10 days per 100 days post-embolization, *P*=0.04). Three quarters of patients with episodes of grade III-IV HE before embolization did not experience any episode of HE post-embolization. Furthermore, the grade of ascites (assessed at 1 and 3 months) and of gastro-esophageal varices (assessed endoscopically after 3 months post-embolization) was comparable to the degrees found pre-intervention. Results of this analysis indicate that selective embolization of SPSSs in this group of cirrhotic patients improves quality of life and health economic balance and does not aggravate portal hypertensive syndrome.

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Please select the one best answer by circling the appropriate letter.

1. Nardelli and colleagues determined that which of the following patient populations should be considered for treatment to prevent overt hepatic encephalopathy (OHE)?

a. All cirrhotics

b. Only cirrhotic patients older than 60

c. Cirrhotic patients with minimal hepatic encephalopathy (MHE)

d. Cirrhotic patients with sarcopenia

2. Regarding prophylactic therapy for the development of recurrent HE:

a. Lactulose and probiotics are equally effective

b. Only lactulose is effective

c. Only probiotics are effective

d. Rifaximin should not be combined with lactulose

3. In cirrhotic patients, which of the following could indicate a patient is at risk for driving errors?

a. Abnormal NCT-A scores

b. > 10-year history of HE

c. High CFF scores

d. High DST scores

4. Which of the following symptoms related to sleep is associated with HE-related neuropsychiatric development?

a. Difficulty falling asleep

b. Frequent night wakenings

c. Nocturia

d. Daytime sleepiness

5. A study by John and colleagues found that which of the following is true with regard to spontaneous spleno-renal shunts (SRS)?

a. SRSs cause portal vein thrombosis (PVT)

b. PVTs are associated with the development of SRSs and subsequent HE

c. SRSs are associated with an increased risk of mortality

d. SRSs can be safely embolized

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	This learning objective did (or will) increase/improve my:	*High Impact*	*Moderate Impact*	*No Impact*	*Not Applicable*
• Identify predictors of hepatic encephalopathy (HE) in patients with cirrhosis and determine appropriate prophylactic regimens for such patients	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Evaluate the use of breath sample analysis to diagnose HE	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Describe specific bacteria that are related to cognition and inflammation in HE	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Determine additional problems that may be associated with neuropsychiatric impairment in HE and assess appropriate screening tools to diagnose these conditions	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Analyze the development of and treatment with portosystemic shunts in HE	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑

Impact of the Activity

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity *(select all that apply)*:

❑ Patient care or patient-centered care
❑ Practice-based learning and improvement
❑ Interpersonal and communication skills
❑ Employ evidence-based practice
❑ Interdisciplinary teams
❑ Professionalism
❑ Quality improvement
❑ Medical knowledge
❑ System-based practice
❑ Utilize informatics
❑ None of the above

- The content of this activity matched my current (or potential) scope of practice.

❑ No _____
❑ Yes, please explain _____

- Was this activity scientifically sound and free of commercial bias* or influence?

❑ Yes _____
❑ No, please explain _____

** Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.*

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	Strongly Agree	*Agree*	*Disagree*	*Strongly Disagree*	*Not Applicable*
• The educational activity has enhanced my professional effectiveness in treating patients	❑	❑	❑	❑	❑
• The educational activity will result in a change in my practice behavior	❑	❑	❑	❑	❑

• How will you change your practice as a result of participating in this activity *(select all that apply)*?

❑ Create/revise protocols, policies, and/or procedures
❑ Change the management and/or treatment of my patients
❑ This activity validated my current practice
❑ I will not make any changes to my practice
❑ Other, please specify: _____

• What new information did you learn during this activity?

_____
_____
_____

• Please indicate any barriers you perceive in implementing these changes.

❑ Lack of experience
❑ Lack of resources (equipment)
❑ Lack of time to assess/counsel patients
❑ Lack of consensus of professional guidelines
❑ Lack of opportunity (patients)
❑ Lack of administrative support
❑ Reimbursement/insurance issues
❑ Patient compliance issues
❑ No barriers
❑ Cost
❑ Other _____

• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients' outcomes?

_____
_____
_____

• Comments to help improve this activity?

_____
_____

• Recommendations for future CME/CPE topics.

_____
_____
_____

To assist with future planning, please attest to time spent on activity:

I spent _____ hours on this program

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Please do not use abbreviations.
We need current and complete information to assure delivery of participation acknowledgement.

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